DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

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Peter O. Safir
Millicent C. Yim
KLEINFELD, KAPLAN AND BECKER
Counsel for Choay S.A.
1140 Nineteenth Street, N.W.
Washington, D.C. 20036-6601

Re: Request for Revision of Regulatory Review Period Determination for Lovenox®
Docket No. 93E-0214

Dear Sirs:

This is to notify you that, after due consideration, the above-referenced Request for Revision of Regulatory Review Period Determination for Lovenox® is hereby denied. The basis for this decision is set forth below.

The request, submitted on behalf of Choay S.A. ("Choay"), states that FDA incorrectly determined the date upon which the New Drug Application ("NDA") for Lovenox® was "initially submitted" for purposes of patent term extension, and therefore incorrectly calculated the lengths of the testing and approval phases of the regulatory review period. Choay states that it believes that the Lovenox® NDA was "initially submitted" on July 26, 1991 (the date the agency acknowledges having received the Lovenox® NDA submission that it refused to file because it was incomplete), and not on December 31, 1991, the date that FDA determined the NDA to be "initially submitted." Choay claims that it "made a deliberate effort to submit an application containing all information necessary for agency review to begin," (See H. Rept. 96-857, 98 Cong. 2d Session 44 (1984))("House Report") and that the NDA "contain[ed] sufficient information to allow FDA to commence review of the application" (See 21 C.F.R. § 60.22(d)). Therefore, Choay argues, even though the NDA was not "filed," it should be considered "initially submitted" as defined in the Act and regulations.

FDA disagrees with Choay's opinion that its NDA, while insufficient for filing was sufficient to be considered "initially submitted," for reasons stated in the paragraphs below. The applicable regulation, 21 C.F.R. § 60.22(d), states that an NDA is "**initially submitted** on the date it contains sufficient information to allow FDA to commence review of the application" (emphasis in original). FDA has determined that "sufficient information" means all information and sections specified in 21 C.F.R. § 314.50. The standard for filing embodies the same concept that an application must contain the information necessary for the agency to commence review of the entire application. Specifically, the filing standard states: "the filing of an application ... means that FDA has made a threshold determination that the application ... is sufficiently complete to permit a substantive review." 21 C.F.R.

§ 314.101(a)(1)

FDA has determined that Choay's July 26, 1991 submission was incomplete because it did not include all required information, as specified in 21 C.F.R. § 314.50. By letter dated September 20, 1991, FDA notified Choay that its NDA was "not sufficiently complete to merit a critical medical and technical review." The letter then listed information that could not be located and described why FDA was refusing to file the NDA under 21 C.F.R. § 314.101(d), outlining the following deficiencies in four different critical sections of the NDA:

Administrative

Case Report Tabulations as required by 21 C.F.R. § 314.50(f)(1).

Clinical

Endpoint assignments as used by the sponsor for data analysis.

Chemistry

1. Process validation data for the aseptic fill.

2. Statistical analysis of the stability data.

Biopharmaceutics

1. Information that links the market image of enoxaparin [Lovenox®] to the product used in clinical trials.

2. Pharmacodynamic data in hepatically impaired patients.

3. Data on metabolism and excretion of enoxaparin.

4. The proposed package insert is inadequately annotated. For example, no reference is given to support the information in the CLINICAL PHARMACOLOGY section that relates to hepatic metabolism of enoxaparin.

5. All foreign language material must be translated as required by 21 C.F.R. § 314.50 (g)(2). Untranslated reports in French from literature have been submitted.

6. The NDA is not indexed in a manner that will permit comprehensive review. The index is not complete in itself, but rather presents a multistep process that crosses many volumes.

Choay claims that the application it originally submitted on June 26, 1991, was complete and only required some additional minor document revision. Specifically, Choay states that during an informal conference with FDA on November 13, 1991, a mechanism for resolving eight out of the ten above deficiencies was agreed to by FDA and Choay. Though a necessary first step, agreeing on how deficiencies will be resolved is separate and distinct from actually resolving them. According to Choay, FDA did not require any additional studies as a condition for NDA resubmission.

Choay states that the two primary reasons for FDA refusing to file its first NDA were: 1) Choay used the name of a domestic supplier of the raw materials for enoxaparin in its NDA rather than the ultimate foreign supplier of the raw materials that had been used to supply the raw materials for the clinical trials because it was a foreign company (deficiency 1 under the Biopharmaceutics section), and 2) the FDA medical reviewer's "preference" that the basis for clinical endpoint assignments for two of the six outcome groups in certain efficiency studies be described in more detail (deficiency under the Clinical section).

However, FDA refused to file Choay's application for Lovenox because of ten separate deficiencies in four different critical areas that prevented the application from having sufficient information to commence review. See 21 C.F.R. § 60.22(d). In its December 31, 1991 submission Choay made the following corrections that were necessary to permit the agency to have sufficient information to commence review of the NDA:

Clinical

Supplemental information was included to explain how patients who did not have a venography were assigned to a positive or negative outcome and the steps taken to minimize bias in making these outcome assignments.

Chemistry

1. Supplemental information on membrane filters and sterile media fill tests was included to provide process validation for the aseptic fill.

2. Supplemental information was included to provide statistical analysis of the stability data, so the agency could determine the adequacy of the methodology.

Biopharmaceutics

1. Choay changed the proposed supplier of the raw materials for the drug product to match the supplier of the raw materials for clinical testing.

2. While FDA did not require Choay to include specific studies of enoxaparin's pharmacodynamic effect in hepatically impaired patients because of the safety concerns for the hepatically impaired volunteers required for the conduct of such a trial, the agency said that data related to dose in hepatically impaired patients who may have been enrolled in the clinical tests would be important to include in the labeling for enoxaparin. Choay agreed to review its study data and identify results specific to hepatically impaired patients.

3. New data were submitted from a recently completed animal study to provide data on metabolism and excretion of the drug to supplement the NDA.

4. The proposed package insert was revised for the informal conference to include proper annotation for the document.

4. All foreign language material was translated into English.

5. The NDA was re-indexed as proposed at the informal conference to provide comprehensive review.

Because agency review required the results of all the corrections listed above, the additional submission was required for the NDA to contain "**all information necessary for agency review to begin.**" 53 Fed. Reg. 7,301 (1988)(quoting H.R. Rep. No. 857, 98th Cong., 2d Sess., pt. 1, at 44 (1984))(emphasis added). Since the NDA was not "initially submitted," the testing phase had not ended until the resubmission along with the originally submitted NDA had been accepted for filing and review. See 21 C.F.R. § 60.22(d); House Report at 2677.[1]

Choay's request then discusses various interpretations as to why the "initially submitted" standard should be separate from the "filed" standard. Specifically, Choay argues that Choay

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[1] "This term ['initially submitted'] is used instead of the term 'filed,' because an application is often not considered to be filed [by FDA], even though agency review has begun, until the agency has determined that no other information is needed...." House Report at 2677.

"made a deliberate effort to submit an application containing all information necessary for agency review to begin" and was "complete enough so that agency action could be commenced." 53 Fed.Reg. at 7302 (quoting the House Report). Choay argues that the application also satisfies the standard in the regulations: "contains sufficient information to allow FDA to commence review of the application." 21 C.F.R. § 60.22(d). Choay also believes that the legislative history demonstrates that the term "initially submitted" should be used to describe the time when the testing phase is completed and the approval phase has begun. House Report at 2677.[2]

Choay's argument that it made a "deliberate effort to submit an application containing all information necessary for agency review to begin" and was "complete enough so that agency action could be commenced" ignores several facts. See 53 Fed.Reg. at 7302 (quoting the House Report). For example, for Choay to have made an effort to submit a complete application, at least all of the foreign language material should have been translated into English as required by 314.101(d)(5) and Choay should have realized that there would be a problem with using a different supplier of the raw material in the clinical trials than in the NDA. See 314.50(d)(1)(ii).

Finally, Choay cites an FDA Guidance document relating to refusals to file, dated July 12, 1993 ("Guidance") as an example of how the refusal to file policy has changed since Congress passed the Patent Term Restoration Act in 1984:

> In the past, decisions to refuse to file an application under 21 C.F.R. § 314.101(d)(3) generally were based on extreme deficiencies, e.g., the total omission of a needed section or the absence of any study that was even arguably an adequate and well-controlled study. More recently, applications have been refused when less extreme deficiencies existed, but when it was clear that the deficiencies were severe enough to make the application not approvable without major modifications.

Regardless of the agency's stance on filing of applications, the applicant bears the obligation to comply with the requirements stated in the regulations. The requirements for filing are designed with the concept of providing sufficient information to permit an agency review of the NDA. See 314.101(a)(1). The agency realizes that additional information may be required after the filing threshold has been reached. This is evidenced by the various amendments received on Lovenox's NDA after it was filed and as intended by the Patent

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[2] The House Report section quoted refers to the fact that FDA has 60 days to determine whether an application will be filed and that if in fact the application is filed, the approval phase should begin with the date the accepted application is received, not when the agency accepts the application for filing.

Term Restoration Act[3], with amendments dated: January 30, February 24, March 26, April 8, May 1 and 12, June 19 and 29, August 11 and 13, November 24, and December 8, 17 and 24, 1992; January 8 and 29, and February 3, 18, and 23, 1993. See March 29, 1993 approval letter for Lovenox.

For the reasons stated, FDA finds that the date of the resubmission, December 31, 1991, correctly represents the NDA "initially submitted" date, and FDA's calculation of the durations of the phases of the regulatory review period for Lovenox® are not in need of revision. Therefore, the request for revision is hereby denied.

Sincerely,

Stuart L. Nightingale

Stuart L. Nightingale, M.D.
Associate Commissioner for Health Affairs

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[3] "The Committee recognizes that the agency receiving the application might decide that it needs additional information or other changes in the application." 53 Fed.Reg. at 7302 (quoting House Report).